DUE: 5-3-01

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
HALLYBONE, Huw, G.
CARPMAELS & RANSFORD
43 Bloomsbury Square
London WC1A 2RA
GRANDE BRETAGNE

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	05.12.2000
Applicant's or agent's file reference: P023888WO	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB00/00176	09/02/2000	26/02/1999

International Patent Classification (IPC) or both national classification and IPC
A61K39/095

Applicant
CHIRON S.P.A. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☒	Certain document cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 26/06/2001.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Favre, N

Formalities officer (incl. extension of time limits)
Digiusto, M
Telephone No. +49 89 2399 8162

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".)*:

Description, pages:

1-33 as originally filed

Claims, No.:

1-42 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 32-39 wtih respect to industrial applicability,

because:

☒ the said international application, or the said claims Nos. 32-39 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:
see separate sheet

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrialapplicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1, 23, 27, 28, 30
Inventive step (IS)	Claims	2-22, 24-26, 29, 31-42
Industrial applicability (IA)	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I
Basis of the opinion

Sequence listing pages 1-17 filed with the letter of 18.04.2000 do not form part of the application (Rule 13ter.1(f) PCT).

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 32-39 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV
Lack of unity of invention

The separate groups of invention are:

I) **Claims 1-26, 32-39 and 40-42 (partially)**

These claims relate to immunogenic compositions comprising a Neisseria antigen, an *oligonucleotide comprising at least on CG motif*, and optionally a second adjuvant.

II) **Claims 27-31 and 40-42 (partially)**

These claims relate to adjuvant compositions comprising an *oligonucleotide comprising at least on CG motif* and a second adjuvant. No antigen is

defined in these claims.

The use of *oligonucleotide comprising at least on CG motif* as an adjuvant for vaccination is state of the art (see Item V). Therefore, claims 1-42 are not so linked as to form a single general inventive concept (Rule 13.1 PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. For the assessment of the present claims 32-39 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2. Document D1 (WO-A-98 18810) relates to oligonucleotides which have a sequence including at least one unmethylated CpG dinucleotide and which are immunostimulatory (page 1, lines 11-13). Moreover, D1 discloses that said nucleic acid sequences can be used to treat, prevent or ameliorate disorders (e.g., a tumour or cancer or a viral, fungal, bacterial or parasitic infection; page 10, lines 16-23). For example, the nucleic acid sequences can be administered to stimulate a subject's response to a vaccine (i.e. as an adjuvant). Finally, D1 explicitly disclose *Neisseria gonorrhoeae* and *meningitidis* as examples for infectious bacteria.

   Document D2 (WO-A-98 49288) discloses a method for prophylactically protecting a mammal, including a human, from infection by a pathogen (page 4, lines 22-27). In said method, a composition comprising an oligonucleotide having CpG motif is used (page 5, line 16). Moreover, D1 discloses that the therein-disclosed methods are useful for preventing or treating pathogenic infections in animals and as

prophylactic or therapeutic approaches to pathogenic infections. Such pathogens include Neisseria spp. (page 12, lines 10-20).

Hence, the subject-matter of independent claim 1, which defines an immunogenic composition comprising a Neisseria antigen and an adjuvant comprising an oligonucleotide having CG motif (=CpG, see page 7, lines 12-16, of the description) is not novel over the disclosures of D1 and D2.
Therefore, independent claim 1 does not meet the requirements of Article 33(2) PCT.

2.1 Dependent claims 2-5, which further define trivial embodiments of the composition of claim 1, do not appear to contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step in the sense of Article 33(3) PCT.

2.2 Dependent claims 6-17 define further embodiments of the composition of independent claim 1 where a second adjuvant is used in addition to the oligonucleotide having CG motif.
In the description, Tables 1 and 2 demonstrate that the combination of a second adjuvant together with the oligonucleotide having CG motif enhances the immune responses, as compared with a composition comprising only an oligonucleotide having CG motif.

The problem to be solved by said claims may therefore be regarded as providing a composition which induces enhanced immune responses, as compared to those obtained using the compositions of D1 or D2.

Document D3 (WO-A-98 55495) relates to immunomodulatory compositions comprising an immunostimulatory oligonucleotide sequence (ISS) which contains at least one CG motif (page 7, lines 14-21). Moreover, D3 discloses that administration of an antigen with an ISS **and** an adjuvant leads to a potentiation of a immune response to the antigen and thus, results in an **enhanced** immune response as compared to that which results from a composition comprising the ISS and antigen alone (page 15, lines 5-8). Thus, D3 provides compositions comprising ISS (oligonucleotide sequence which contains at least one CG motif),

an antigen and an adjuvant whereby the ISS/antigen/adjuvant are co-administered, and where the immunogenic composition contains an amount of an adjuvant sufficient to potentiate the immune response to the immunogen. Furthermore, D3 explicitly disclose several particular adjuvants including oil-in-water emulsions, water-in oil emulsions, alum (aluminum salts), liposomes, microparticles, squalene mixtures (SAF-1), muramyl peptide, saponin derivatives, mycobacterium cell wall preparations, monophosphoryl lipid A, mycolic acid derivatives, nonionic block copolymer surfactants, Quil A, cholera toxin B subunit, polyphosphazene and derivatives, immunostimulating complexes (ISCOMs), lipid-based adjuvants and Freund's adjuvant (both complete and incomplete) (page 15, lines 13-25).

Following the disclosure of D3, the person skilled in the art would combine the teachings of said document with D1 or D2, thus obtaining the composition defined in claims 6-17.
Said claims 6-17 are thus not inventive in the sense of Article 33(3) PCT.

2.3 Dependent claims 18-22 define further embodiments of the composition of independent claim 1 comprising particular oligonucleotides having CG motif. Said particular oligonucleotides are not associated with surprising or unexpected effects as compared to those disclosed in D1-D3.
Therefore, the subject-matter of claims 18-22 is not inventive in the sense of Article 33(3) PCT.

2.4 Independent claim 23 differs from independent claim 1 in that it defines a vaccine composition instead of an immunogenic composition (see also Item VIII). However, both D1 and D2 refer to vaccines. Thus, the subject-matter of claim 23 is not novel in the sense of Article 33(2) PCT.

2.5 In the light of the objections put forward under points 2.-2.4, dependent claims 24-26 do not appear to contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step in the sense of Article 33(3) PCT.

2.6 Independent claim 32 and claim 33 define methods of stimulating an immune

response in a host animal using any one of the compositions defined in claims 1-22.
In the light of the objections put forward under points 2.-2.4, the subject-matter of said claims is not inventive in the sense of Article 33(3) PCT.

2.7 A similar objection also applies for the methods defined by independent claim 34 and claims 35-36 as well as those defined by independent claim 37 and claims 38-39.
Claims 34-39 thus do not meet the requirements of Article 33(3) PCT.

3. Independent claim 27 defines an adjuvant composition comprising an oligonucleotide having at least one CG motif and complete Freund's adjuvant.

Document D3 discloses the administration of an antigen with an ISS (oligonucleotide having at least one CG motif which are known in the art as adjuvant, see D1 and D2) **and** an additional adjuvant, which can be complete Freund's adjuvant (page 15, lines 5-25). In other word, D3 discloses an adjuvant composition comprising an oligonucleotide having at least one CG motif and complete Freund's adjuvant.
The subject-matter of independent claim 27 is thus not novel in the sense of Article 33(2) PCT.

3.1 Moreover, D3 also discloses composition comprising ISS with phosphorothioate backbones (page 29, line 3) and having 2 purines and 2 pyrimidines immediately next to the CG motif (page 7, lines 14-21).
Dependent claims 28 and 30 are thus also not novel in the sense of Article 33(2) PCT.

3.2 Dependent claims 29 and 31 define further embodiments of the composition of independent claim 27 comprising particular oligonucleotides having CG motif. Said particular oligonucleotides are not associated with surprising or unexpected effects as compared to those disclosed in D1-D3.
Therefore, the subject-matter of claims 29 and 31 is not inventive in the sense of Article 33(3) PCT.

4. Finally, in view of the above objections, claim 40 which defines a composition identical to those of claims 1-29 (see also Item VIII) and claims 41-42 which define trivial uses of said composition are not inventive in the sense of Article 33(3) PCT.

Re Item VI
Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO-A-99 58683	18.11.1999	07.05.1999	13.05.1998*

Should the present application enter the national or regional phase, the above cited document would be relevant for the question of novelty. Said document discloses the use of Neisseria antigen with immunomodulatory oligonucleotides comprising CG motifs (page 36, lines 15-17).

*Validity of the claimed priority has not been checked.

Re Item VIII
Certain observations on the international application

1. Although claims 1 and 23 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only in respect of the terminology used for the features of that subject-matter (see also claim 42). The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection.

Hence, claims 1 and 23 do not meet the requirements of Article 6 PCT.

2. Claim 40 has been read as relating to a use as a pharmaceutical.

3. The expression "immunostimulating agent" does not have a well-recognised meaning in the art. Claim 15 is thus unclear in the sense of Article 6 PCT.

4. A patent application should be self-contained. Therefore, references to other documents as being "incorporated by reference", e.g. page 3, should be deleted. Moreover, referring to other documents in the claims is deemed to be unclear in the sense of Article 6 PCT. The technical features required should be explicitly incorporated, as said claims should explicitly contain all the essential technical features (Article 6 and Rule 6.3(b) PCT).

5. Claim 17 refers to itself and is thus unclear (Article 6 PCT).

6. The vague and imprecise statements in the description on pages 22, lines 4-5 and 33, lines 36-37, imply that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).